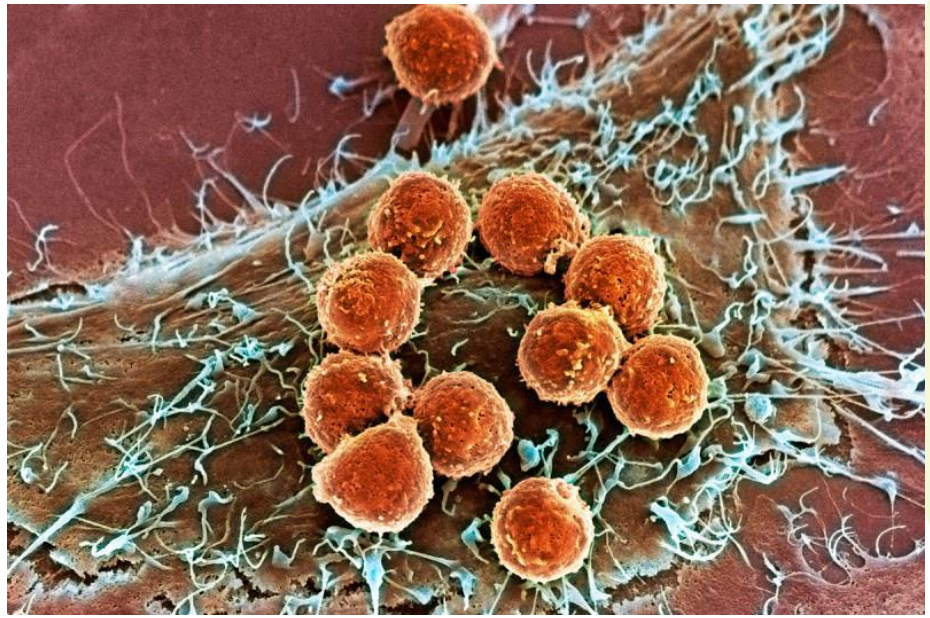
Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy



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Associate Professor with Tenure

The University of North Carolina at Chapel Hill

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

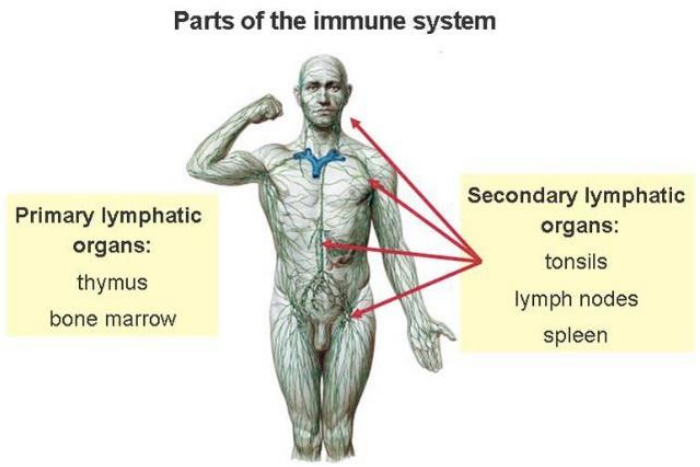
HOPA Hematology/Oncology Pharmacy Association

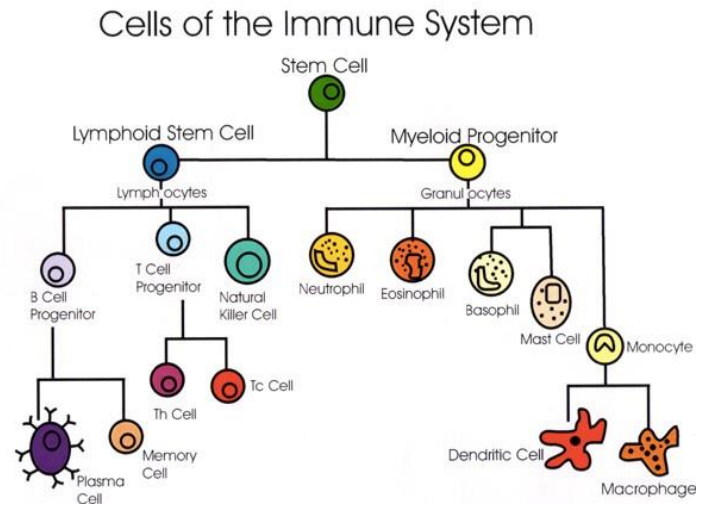
Society for Immunotherapy of Cancer

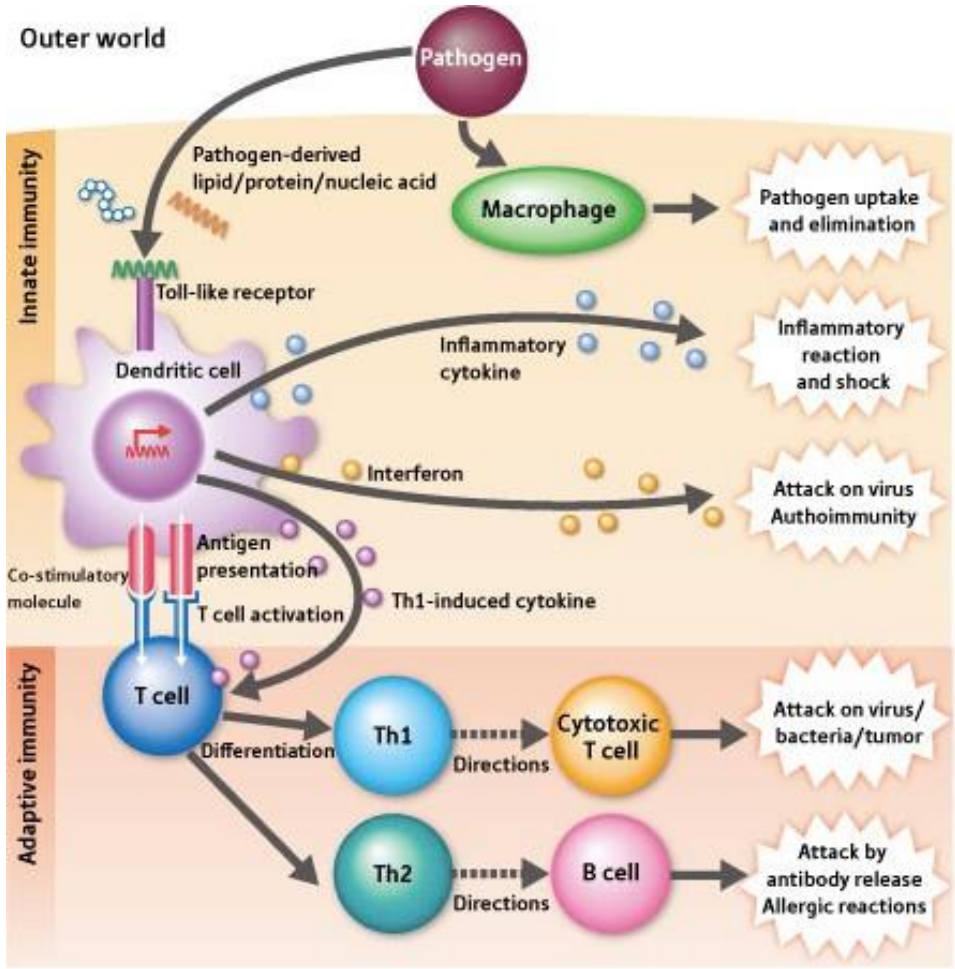
Disclosures

- Contracted Research: Amgen, Merck, SYNDAX Pharma, TerSera/Lexicon
- Consulting Fees: EMD Serono, Novartis, Sanofi
- I will not be discussing non-FDA approved indications during my presentation.

Immune System is Complex



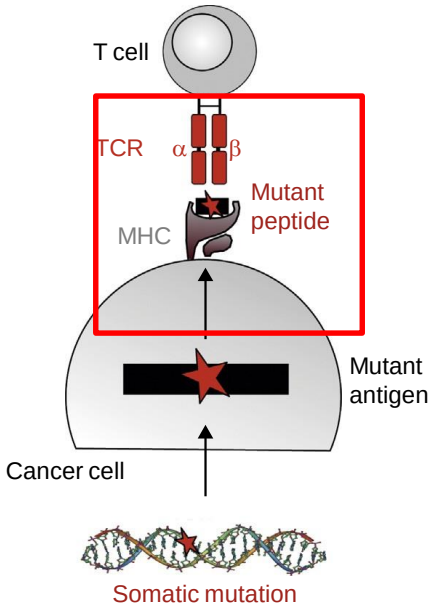




- Recognize and help to adapt
- Kill without good knowledge
  (learning takes time, but time is precious because threat is imminent)

- Learn first, then kill
  (time is **not** precious)

How and What Does the Immune System Recognize (Signal 1)?



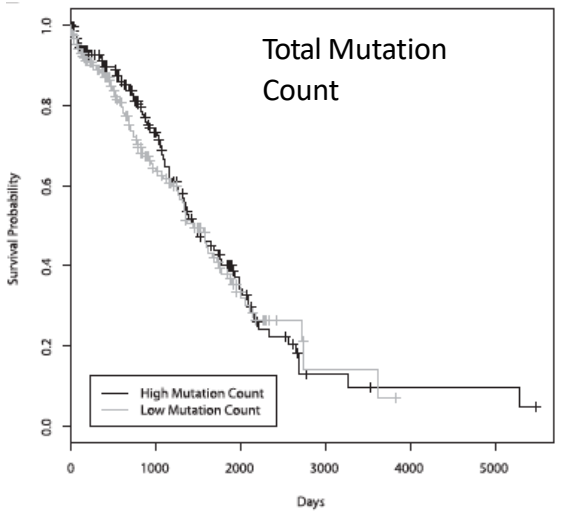
Immune system recognizes bits and pieces of molecules (peptides, lipids, nucleic acid), NOT whole structures

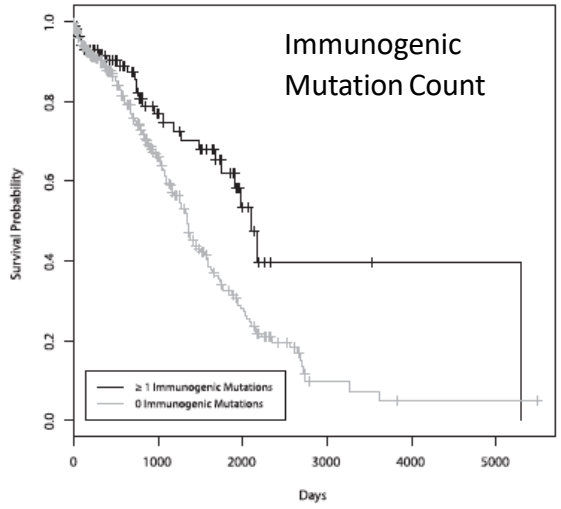
Immune system can respond to non-self antigens but its strength of response depends on:

1. Antigen expression level (not all mutations are expressed)
2. Peptide trimming and transport (antigen processing)
3. Affinity with MHC complex molecule (IC50 <100nM; not all mutations are immunogenic)

Immune system can respond to self antigens, even if no mutation

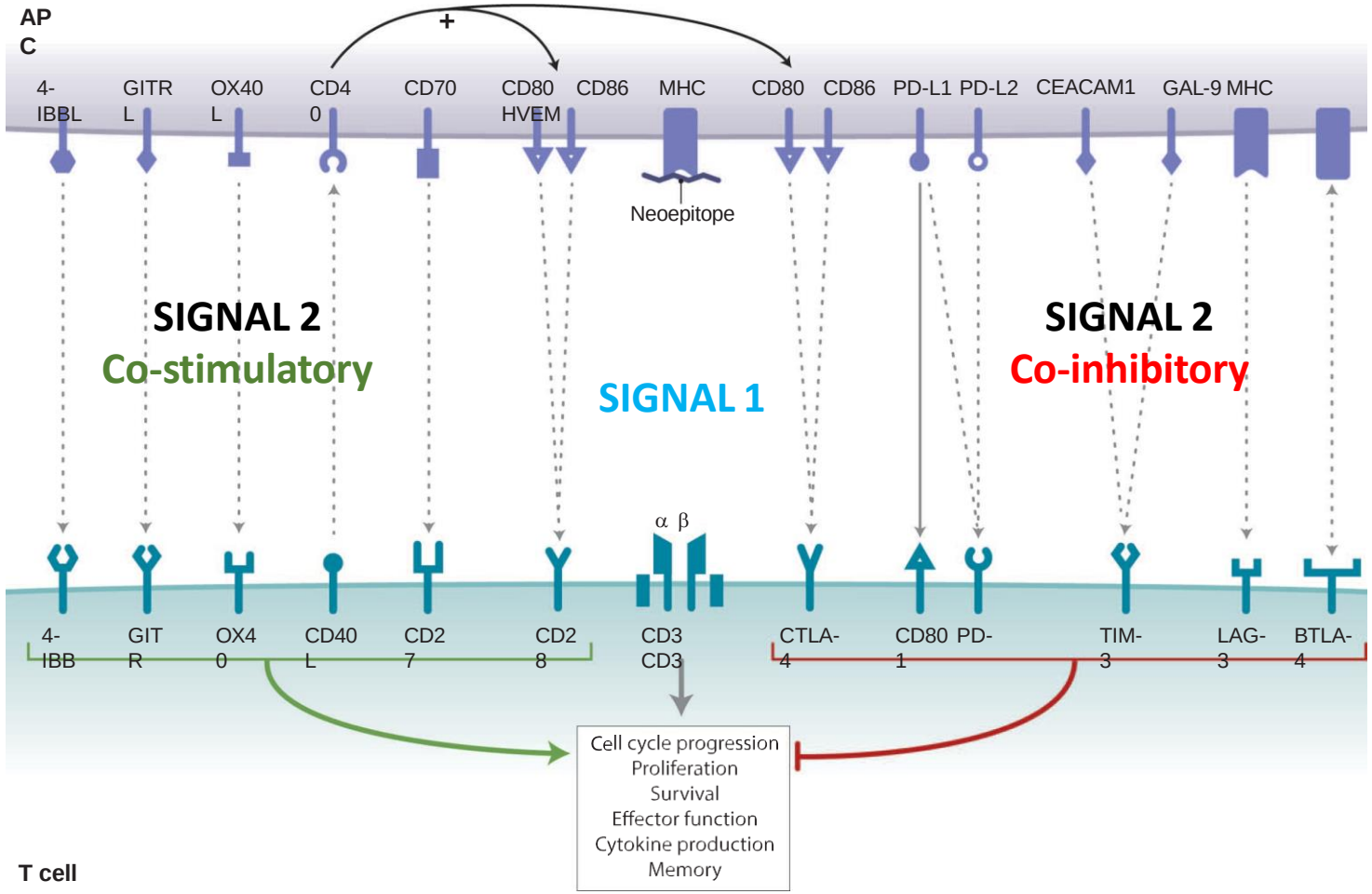
1. If self antigen is expressed in high levels when it is not supposed to (e.g. melanocyte, cancer testis antigens) due to epigenetic changes (methylation, histone acetylation, aberrant splicing)
2. If T cell clones against self antigens are not deleted and are at sufficient numbers (autoimmunity)





Brown et al., Genome Res. 2014

Is Signal 1 Sufficient For Effective Immune Response? Signal 2 Profile is More Crucial



Immune Dysfunction in Signal 2 can occur if:

A. A cancer cell plays the role of an antigen-presenting cell

B. Multiple co-inhibitory immune checkpoint ligands/receptors are upregulated in APC/cancers and T cells

Lesokhin et al., Sci Transl Med. 2015

Antigen-specific T cell Activation is Dependent on 3 Signals!

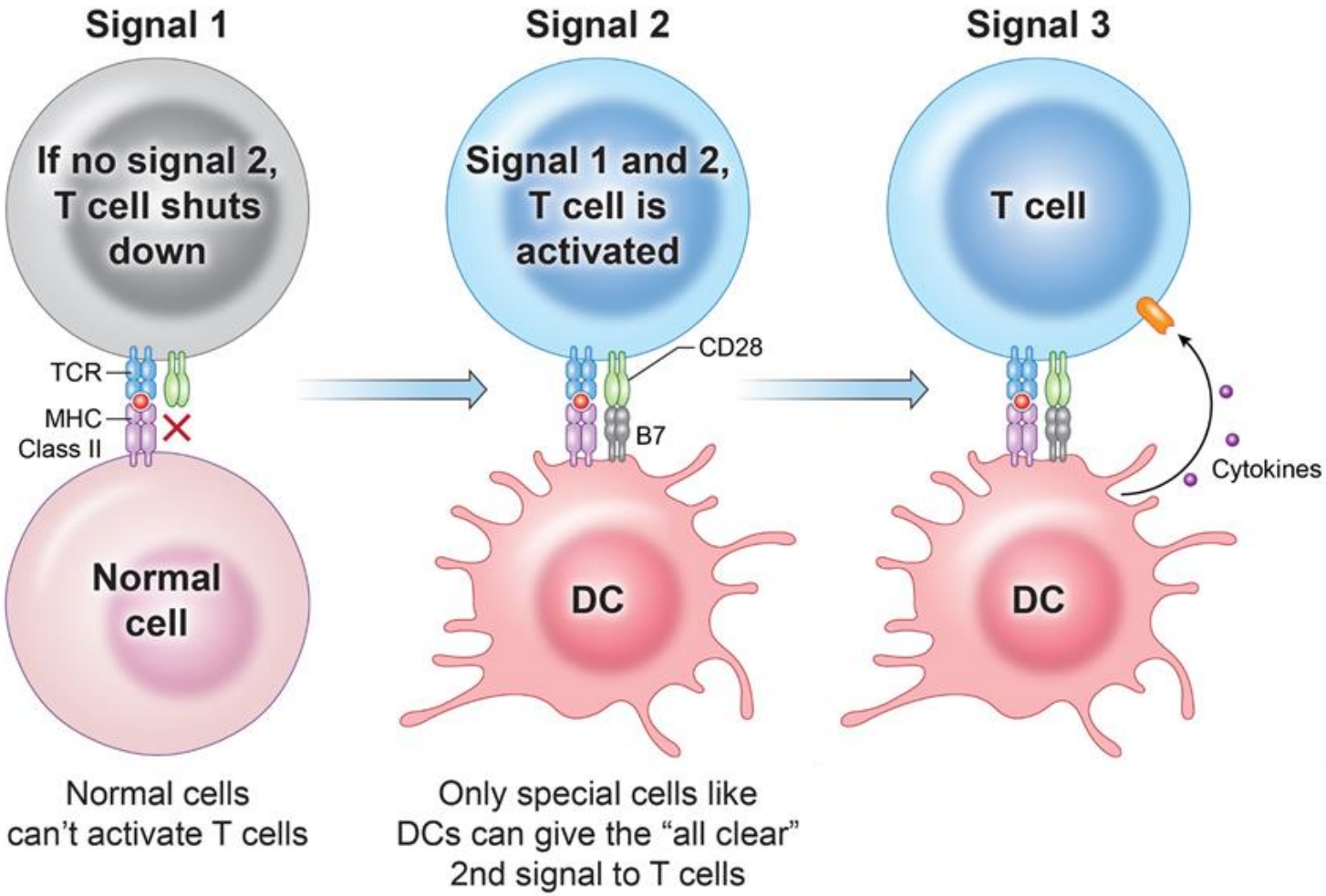
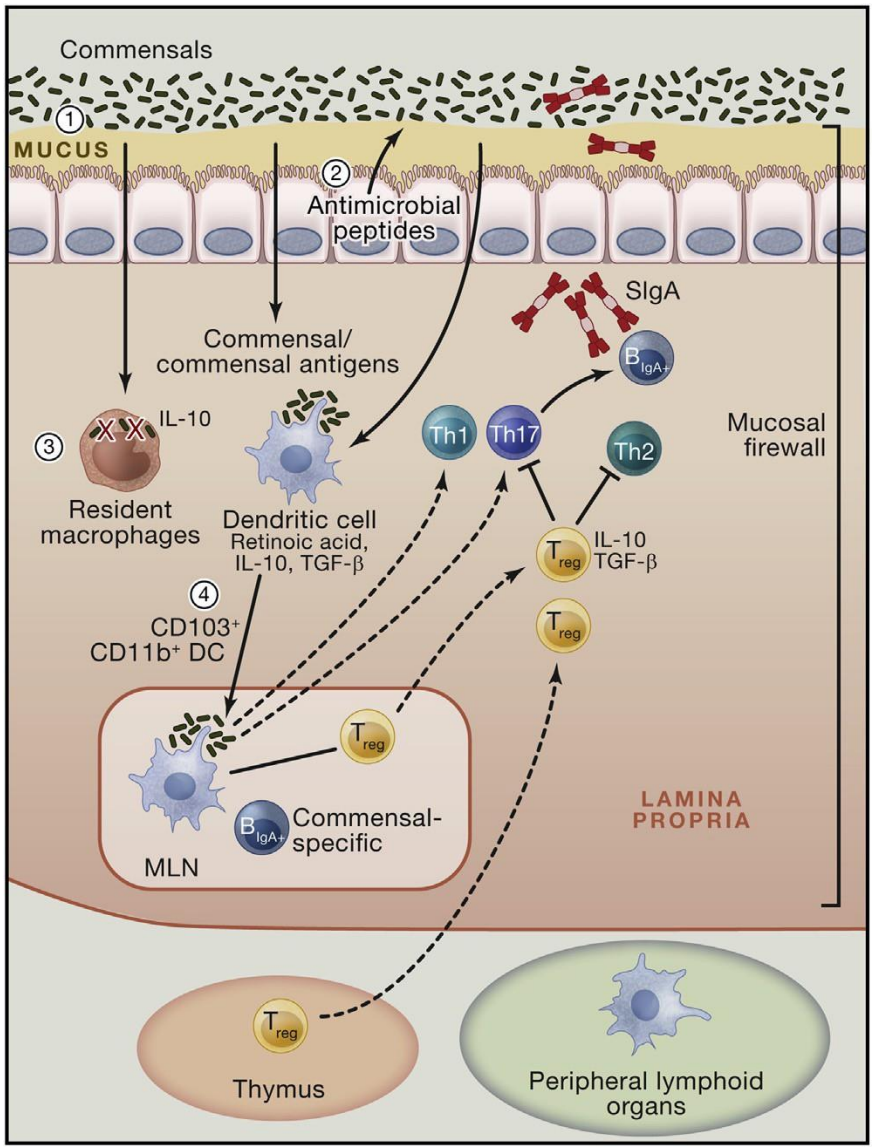


Image courtesy of NCI

Role of Environmental Factors (diet, exercise) on Host Immunity and Signal 3 via the Gut Microbiome

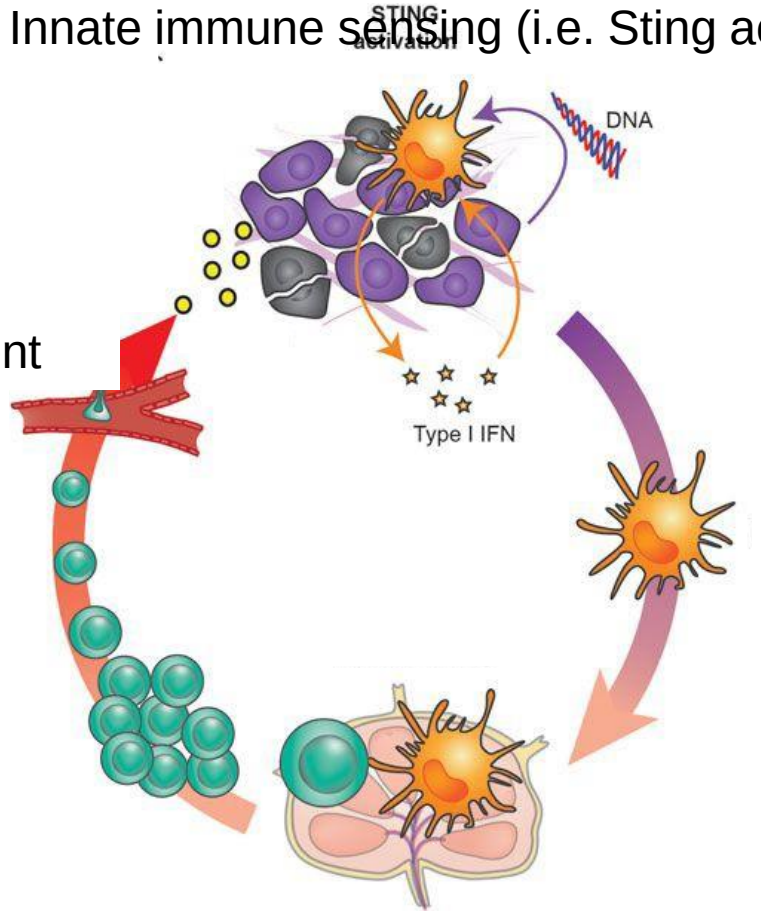


Belkaid et., Cell 2014

Initiation of an Anti-tumor Immune Response

Innate immune sensing (i.e. Sting activation)

T cell recruitment



APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

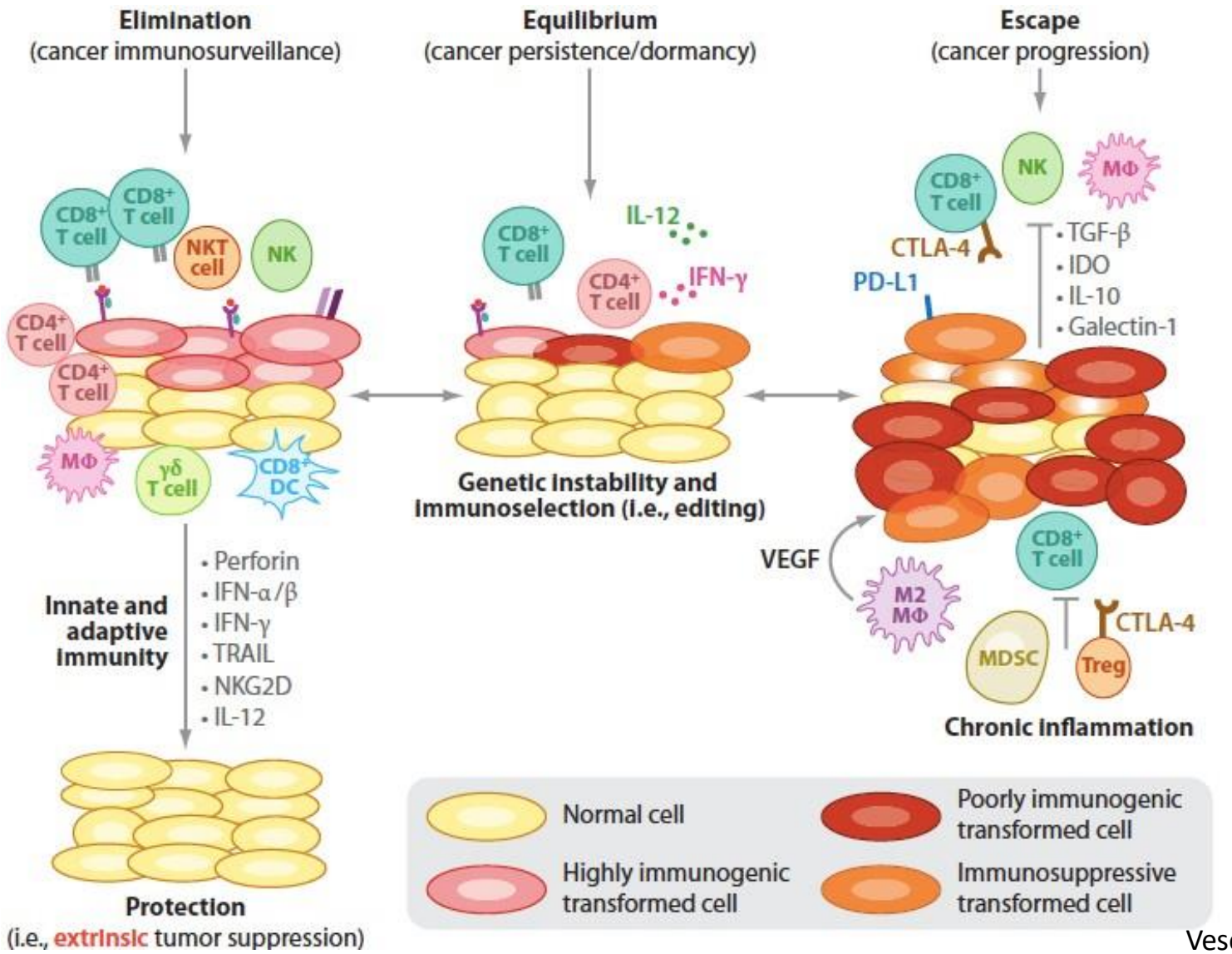
The Premise of Cancer Immunotherapy

- Normally, the immune system eliminates damaged cells, including precancerous and cancer cells

- To escape, tumors evolve mechanisms to locally disable the immune system.

The goal of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.

Cancer Immunoediting-The 3 Es



Vesely et al., Annu. Rev. Immunology 2011

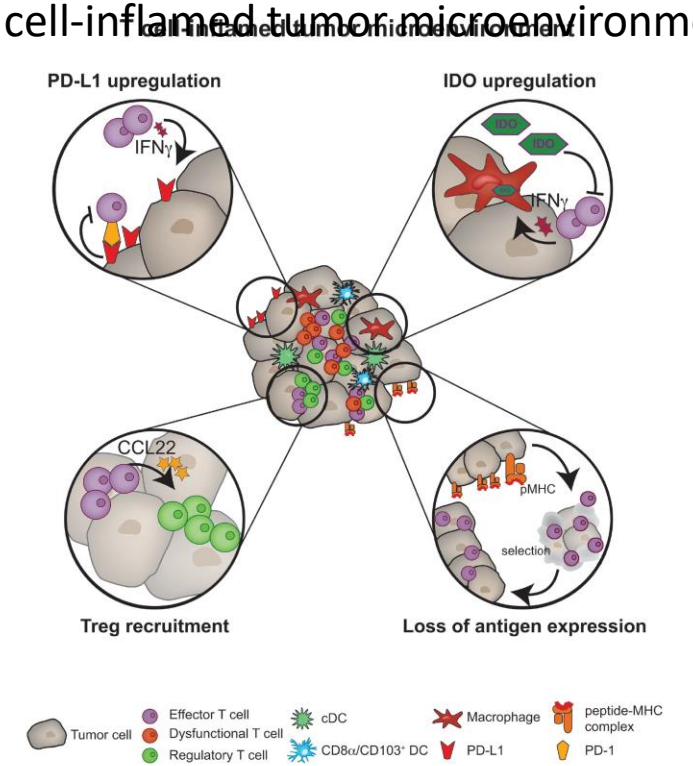
Two Major Mechanisms of Tumor Immune Escape

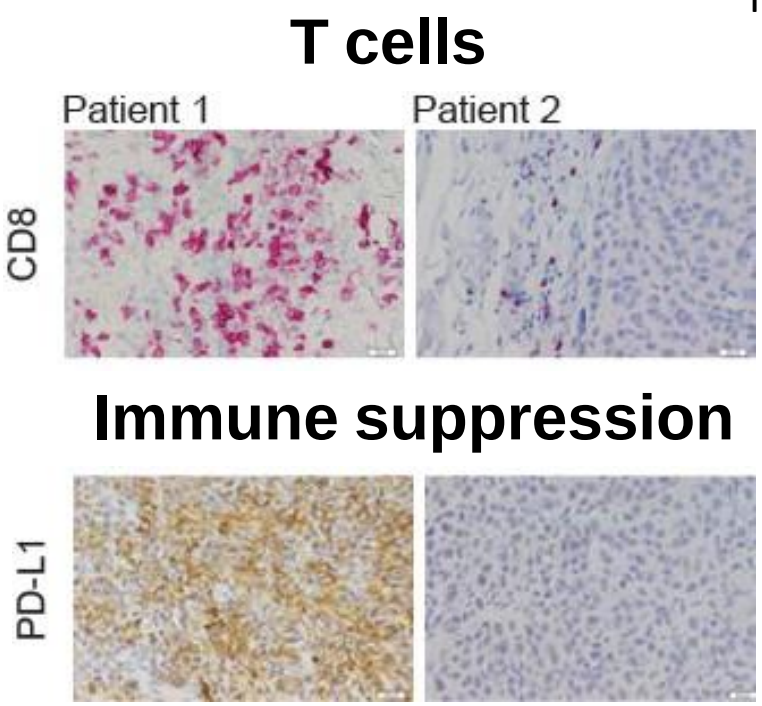
- **Render the immune response dysfunctional:** cytotoxic (CD8+) T cells often become dysfunctional or exhausted during chronic stimulation (chronic viral responses or responses against tumors). To enhance T cell dysfunction, the tumor microenvironment upregulates a suite of suppressive molecules.

- **Avoiding an immune response:** A state in which the tumor remains invisible to the immune system. Many features of tumors can result in immune exclusion/avoidance including lack of antigens (T cells don't "see" anything on the tumor) or active immune repellents.

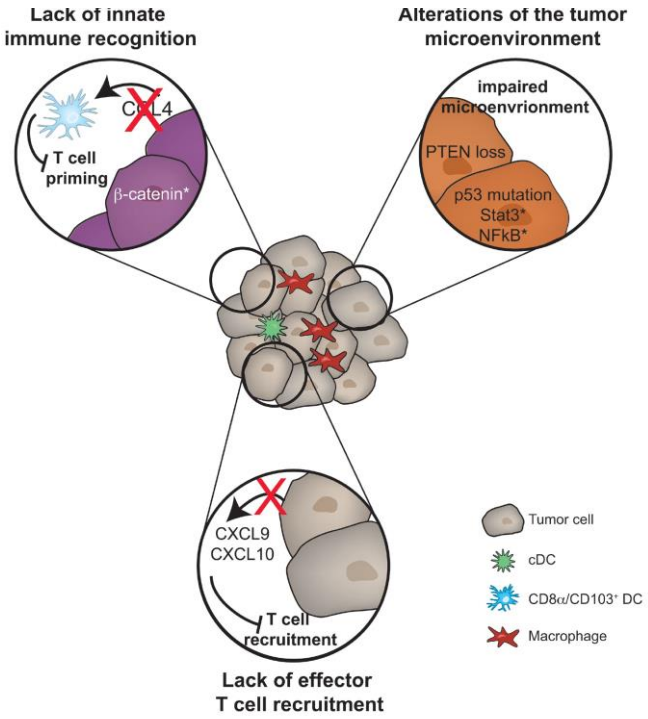
The Outcome of Immune Evasion Are Two Different Outcomes (inflamed and non-inflamed)

T cell-inflamed tumor microenvironment





Non-T cell-inflamed tumor microenvironment



Spranger et al., STM 2013
Spranger, Internat Immunol. 2016

Types of Immunotherapy

- Checkpoint blockade immunotherapy
- Cancer vaccines
- Adoptive cell transfer
- Effector antibodies
- Innate immune activation

The CTLA-4 Checkpoint

Cytotoxic **T**-**L**ymphocyte **A**ssociated Protein **4**

Up-regulated in response to T cell activation

Limits positive stimulation by competition

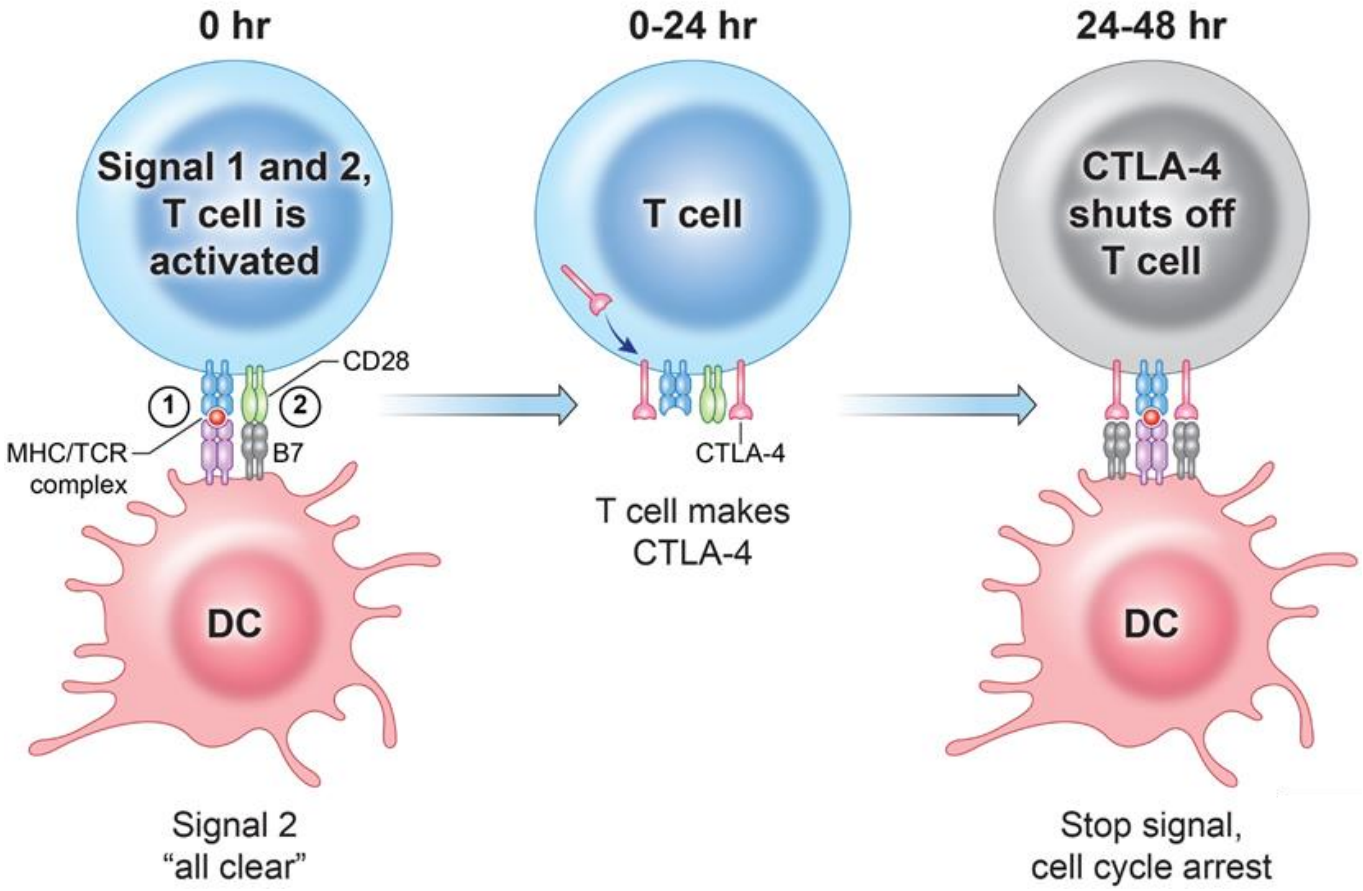


Image courtesy of NCI

The PD-1/PD-L1 Checkpoint

Programmed **D**eath **1**

Up-regulated in response to T cell activation

Ligands PD-L1 and PD-L2 are up-regulated following inflammation (IFNγ)

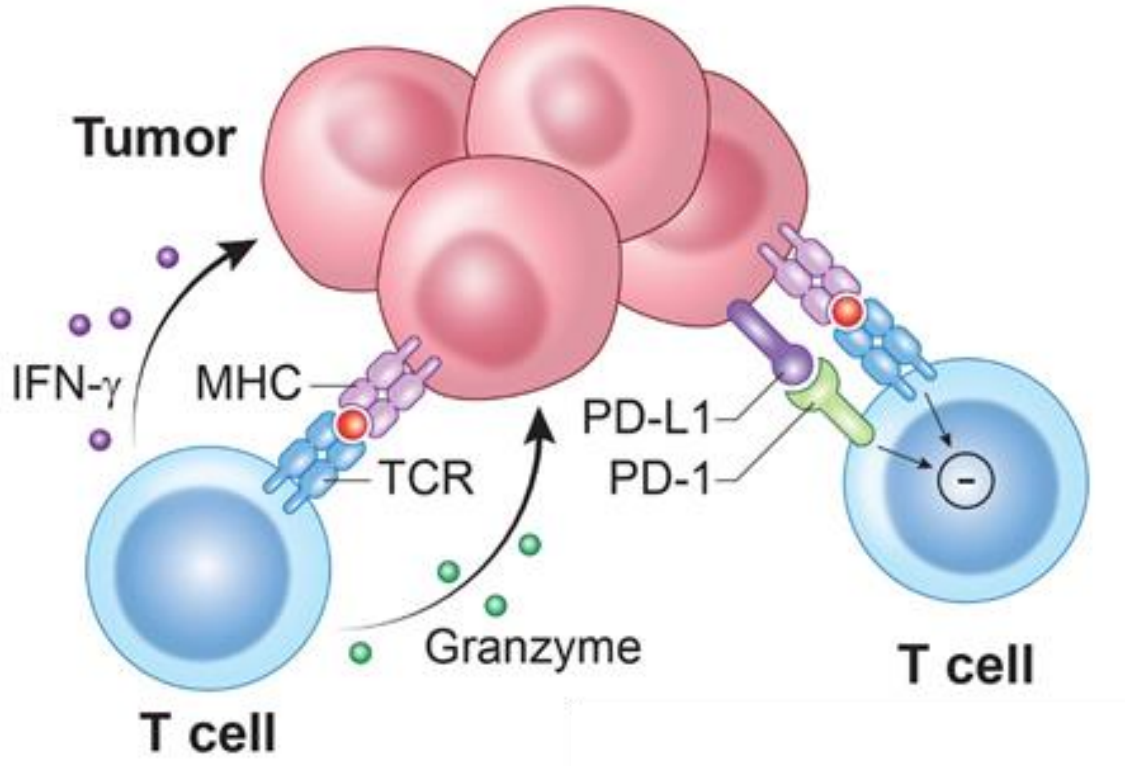
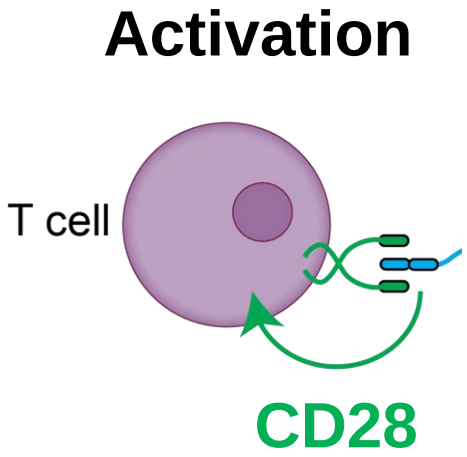


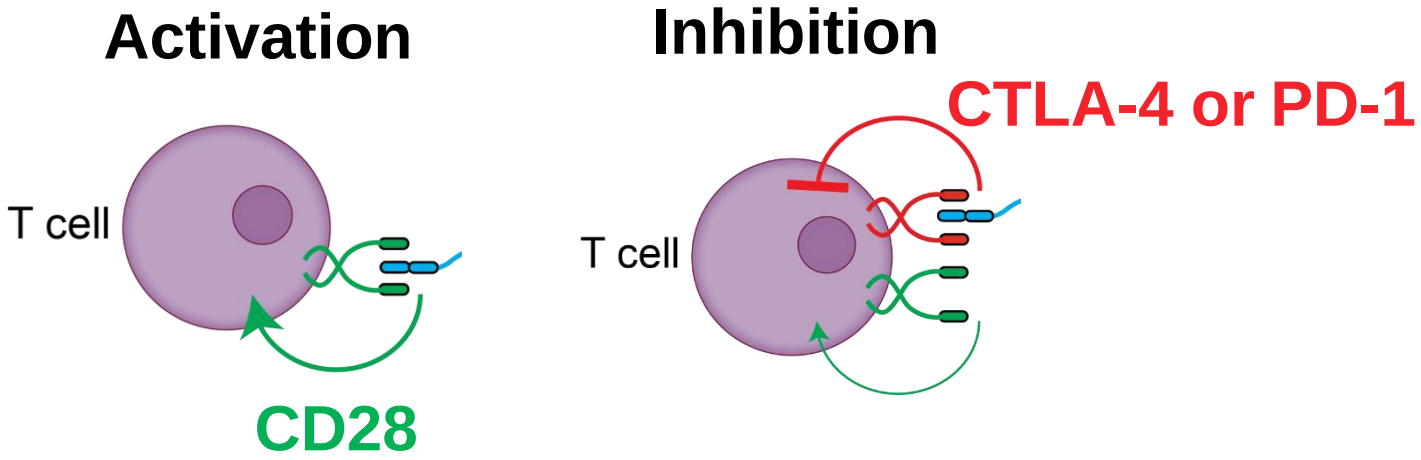
Image courtesy of NCI

Checkpoint Blockade Therapy Unleashes the ”Brakes” on T cells



Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint Blockade Therapy Unleashes the "Brakes" on T cells



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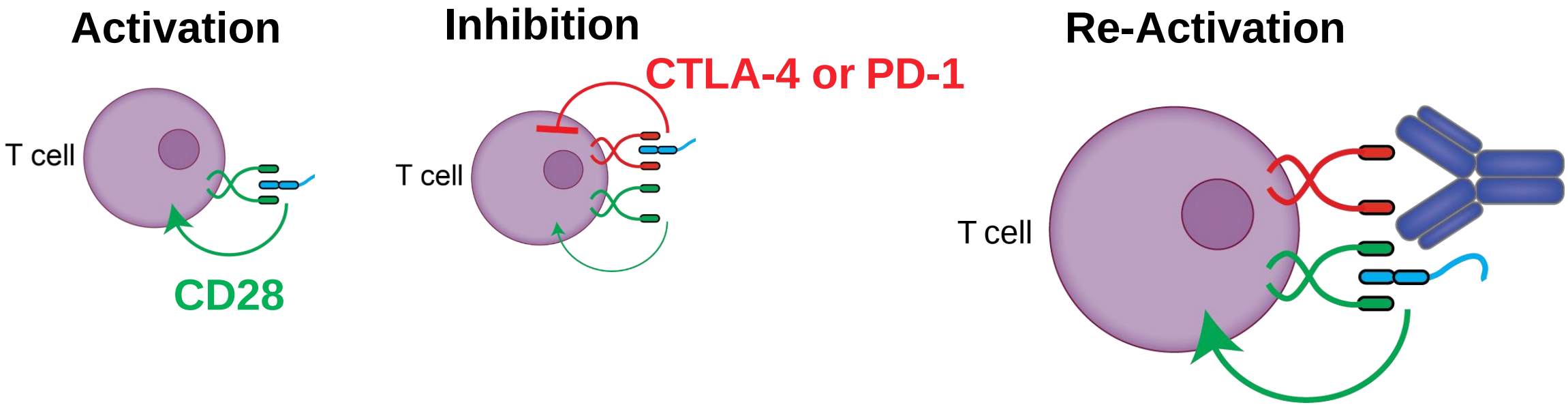

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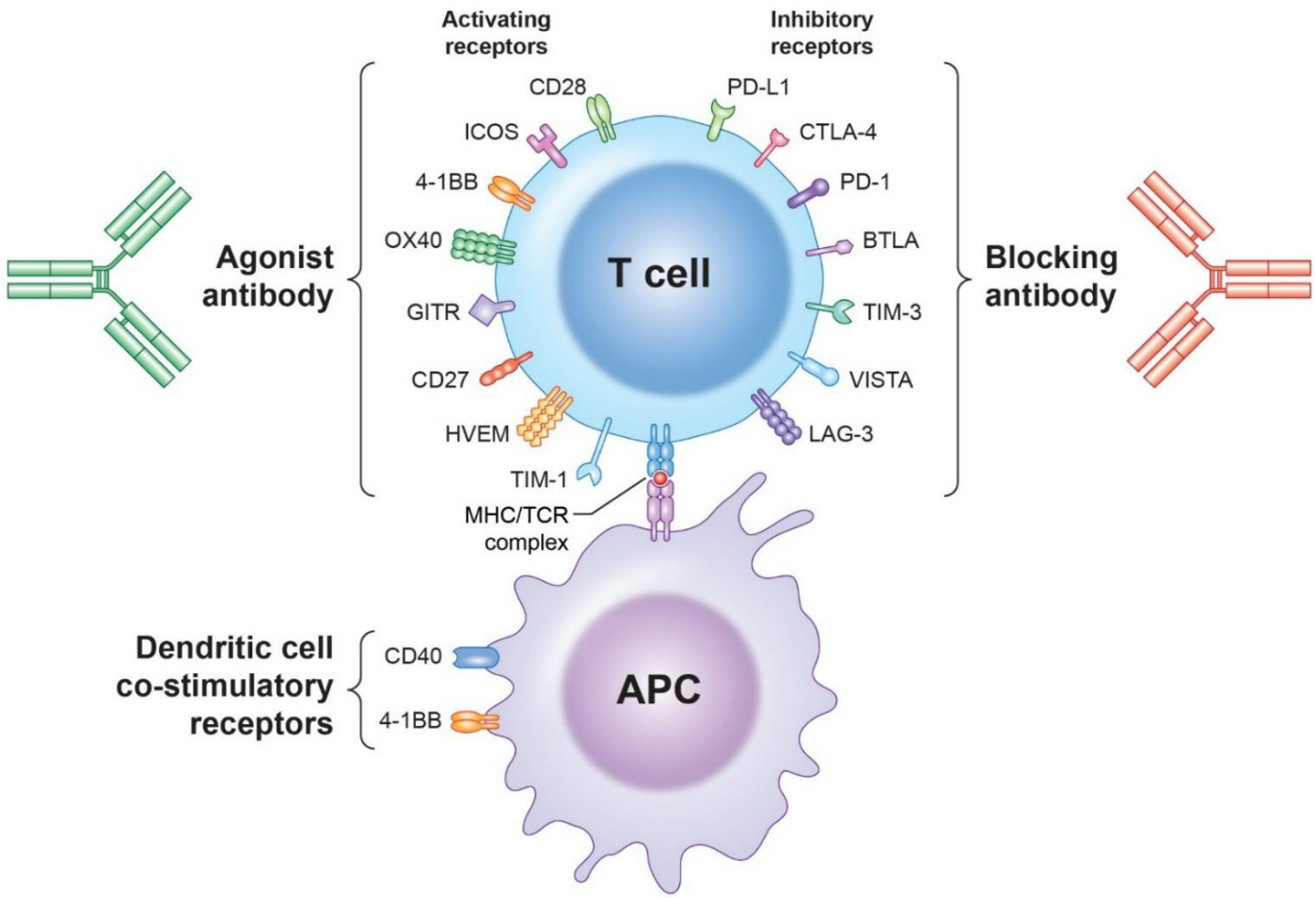
T Cell Checkpoint Modulation

- First generation of checkpoint modulation: blocking inhibitory checkpoints

- Second generation of checkpoint modulation: activating stimulatory checkpoints



Concern 1: is the particular immune checkpoint pathway deregulated for the given cancer?
Concern 2: is there pre-existing host immune response to begin with?

Image courtesy of NCI

Therapeutic Cancer Vaccines

Goal: to increase the immunogenicity of tumor antigens in order to generate a high frequency of tumor-specific T cells.

Concern 1: are the tumor antigens against which we vaccinate clinically important (expressed, biological significance)?

Concern 2: does the vaccine mount high degree of durable responses

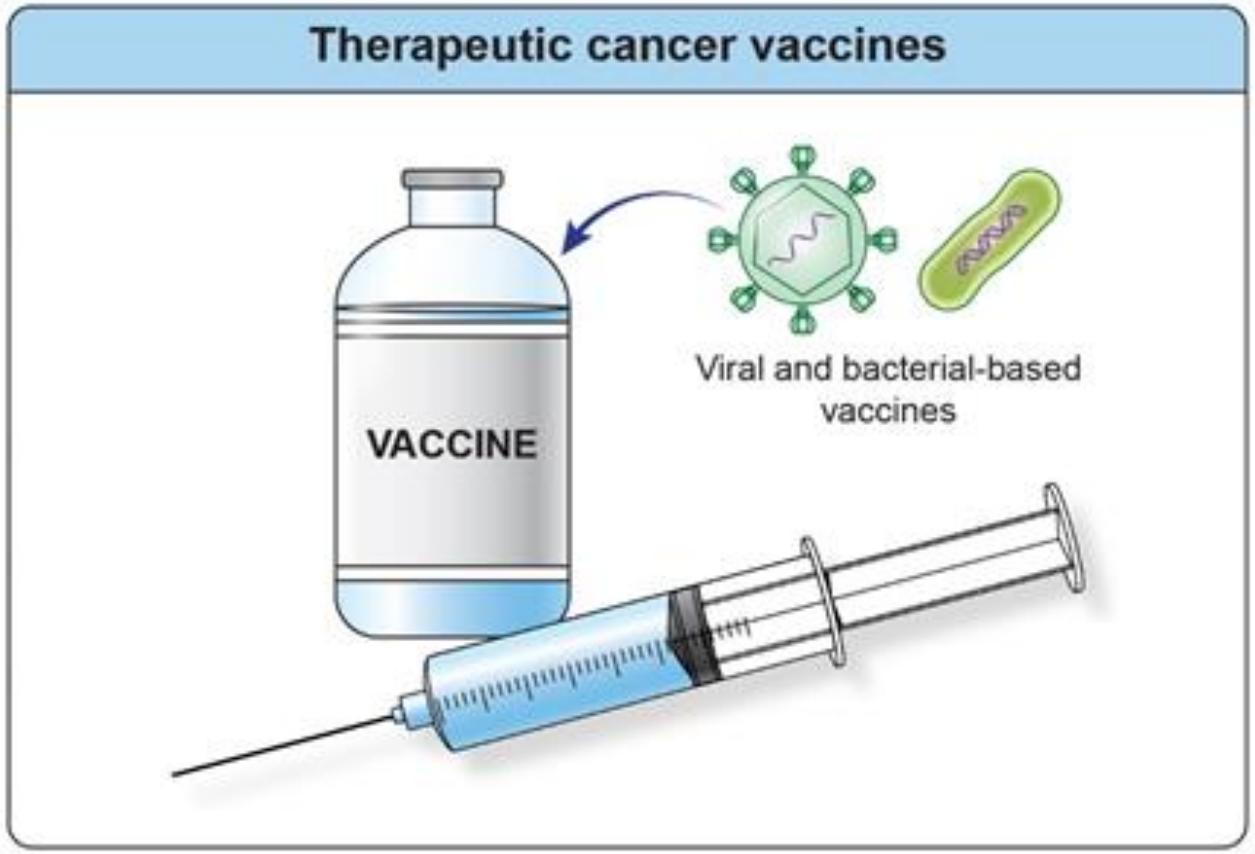


Image courtesy of NCI

Adoptive Cell Therapy

Goal: overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer.

We are either agnostic about the important tumor antigens or we target particular antigens

We need to make space space for these cells so as not to compete with other lymphocytes ("cytokine sink")

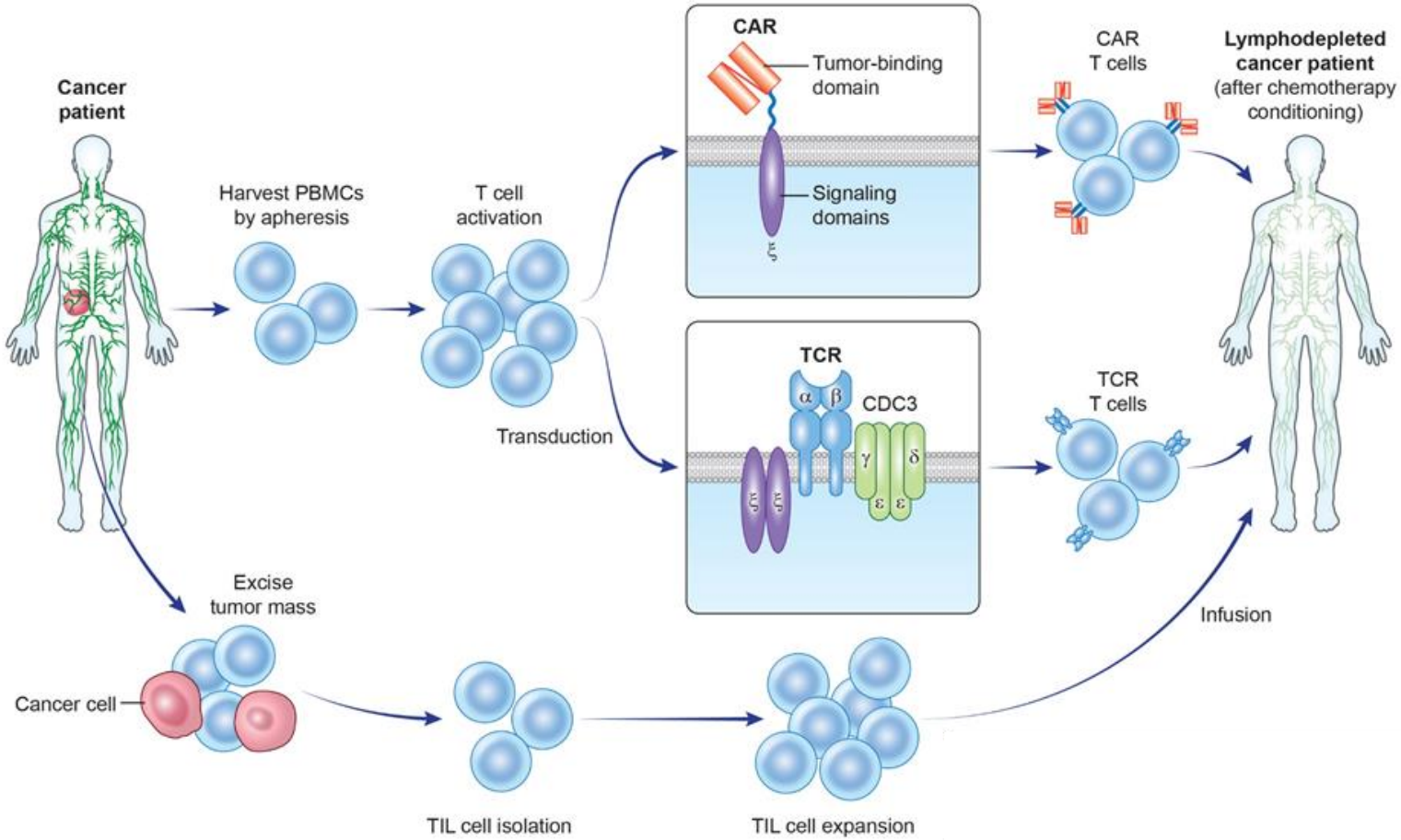


Image courtesy of NCI

Concern 1: Does the tumor have tumor-infiltrating lymphocytes?

Concern 2: Is the particular antigen we target clinically important?

Effector Antibodies and Antibody-Drug Conjugates (ADCs)

Goal: specifically target and kill tumor cells using innate mechanisms which are difficult to evade or suppress and/or through delivery of cytotoxic agents

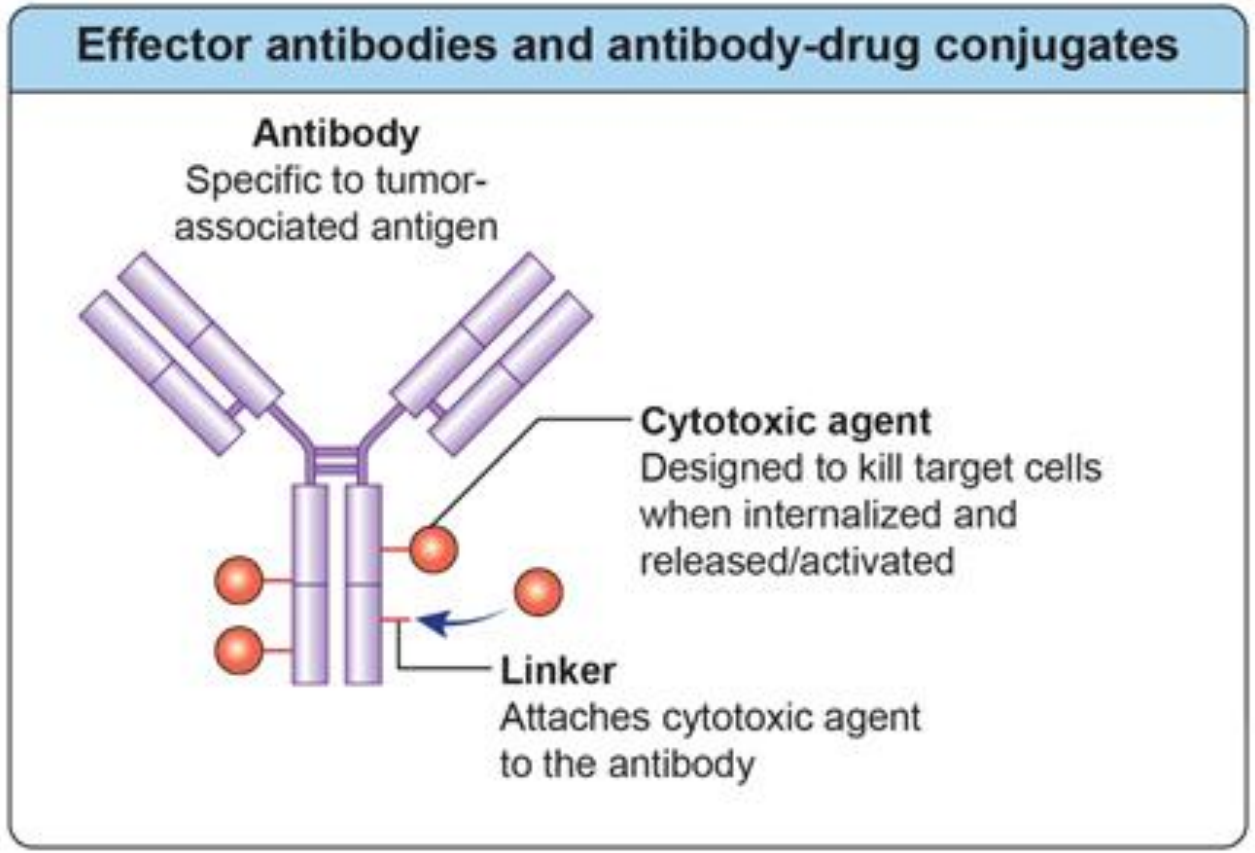
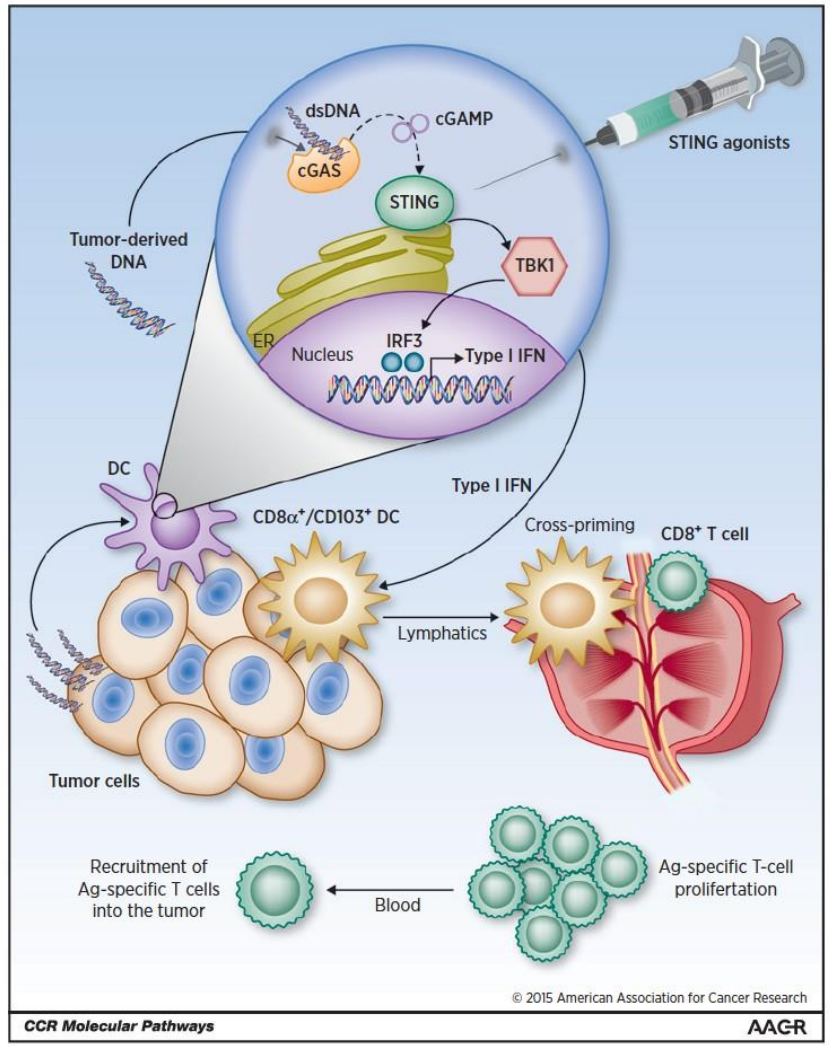


Image courtesy of NCI

Innate Immune Activation

Goal: enhance innate immune sensing by providing stimulatory agents (frequently into the tumor itself)

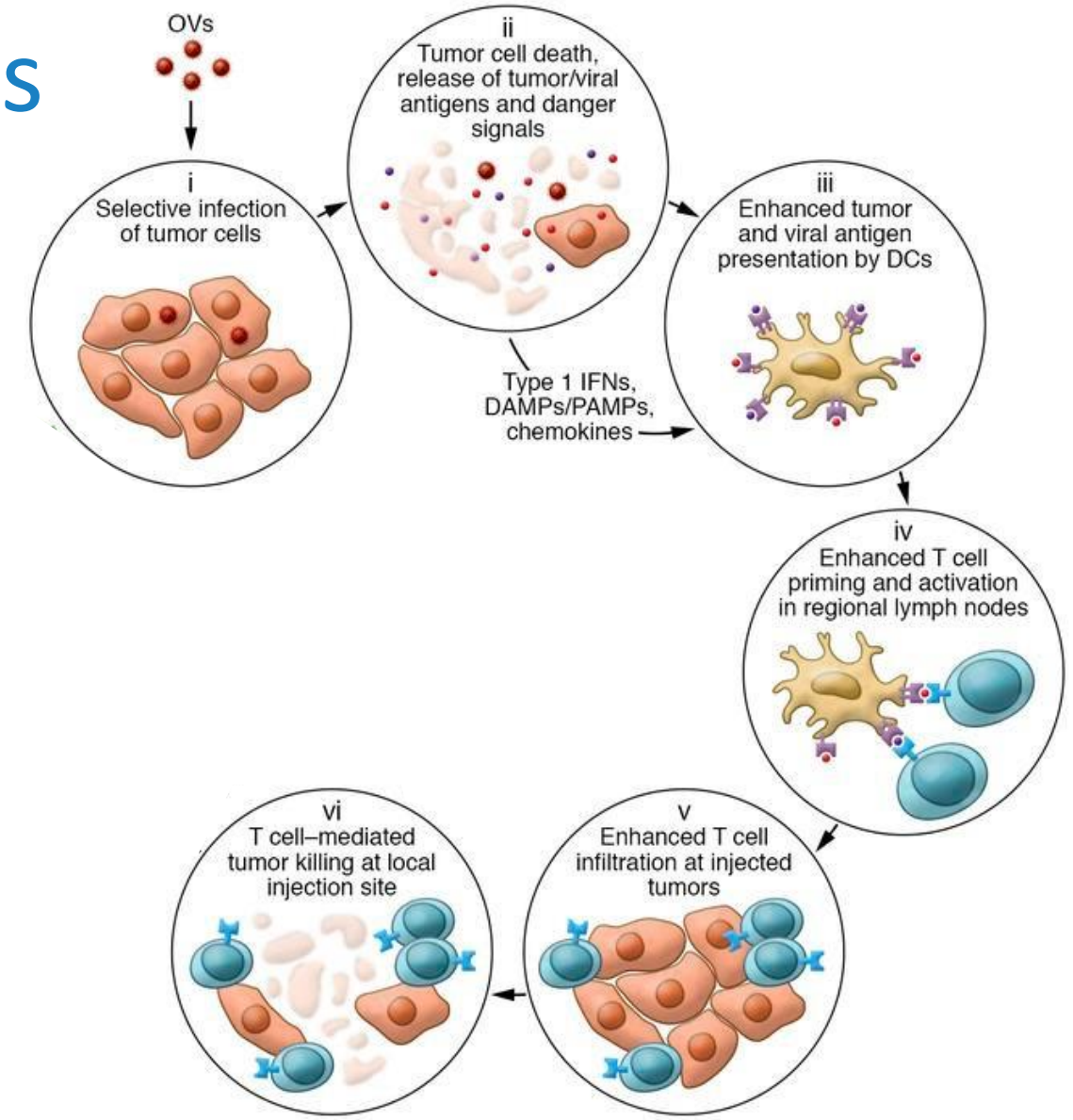


Agents:
Sting agonists
TLR agonists
Immunogenic RNA
Fecal Transplant

Corrales, Clin Can Res 2015

Oncolytic Viruses

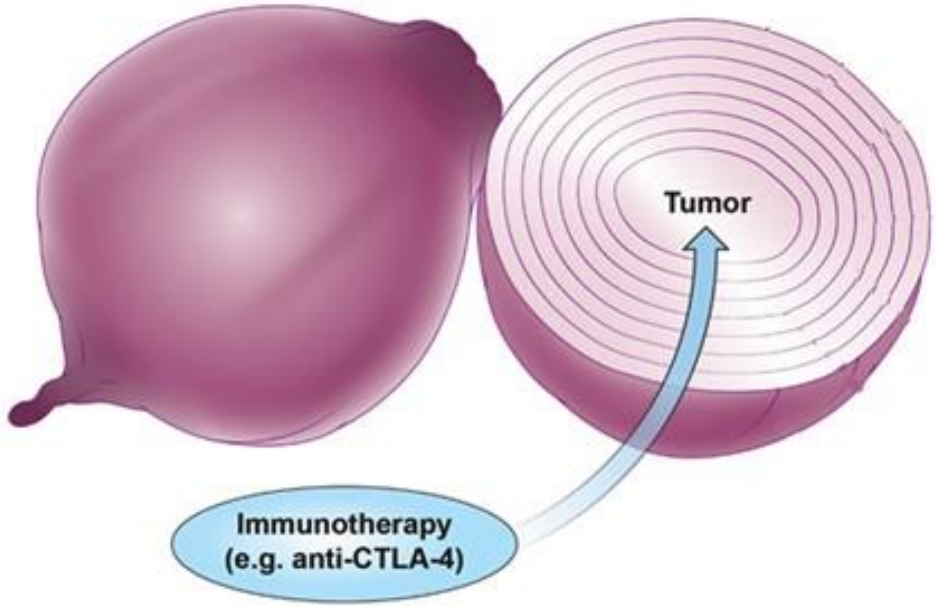
Goal: specifically target and kill tumor cells through viral replication AND release innate immune activators and tumor antigens



Modified from Bommereddy et al. JCI 2018

Multi-layered Immunosuppression

- Tumors insulate themselves with dense layers of immune-suppression
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression
- Combination therapy might be needed to overcome all layers



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Combination Immunotherapies